Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

January 10, 2011

"Boxed" Recommendations

Many recommendations included in the January 10, 2011, edition of the DHHS ***Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*** are presented in "boxes" at the beginning of sections or subsections of the Guidelines. This document is a compilation of all "boxed" recommendations included in the Guidelines. The "boxed" recommendations are presented by section, or section and subsection, as they appear in the Guidelines.

Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy

(Updated January 10, 2011)

DRUG-RESISTANCE TESTING (Updated January 10, 2011)

Panel's Recommendations:

- ***HIV drug-resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether antiretroviral therapy (ART) will be initiated immediately or deferred (AIII). If therapy is deferred, repeat testing at the time of ART initiation should be considered (CIII).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naïve patients (AIII).***
- ***Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers may wish to supplement standard genotypic resistance testing with genotypic testing for resistance to this class of drug (CIII).***
- ***HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ARV regimens in persons with virologic failure and HIV RNA levels >1,000 copies/mL (AI). In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered (BII).***
- ***Drug-resistance testing should also be performed when managing suboptimal viral load reduction (AII).***
- ***In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include a drug from this class in subsequent regimens (BIII).***
- ***Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy (AII).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens (AIII).***
- ***Addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to protease inhibitors (PIs) (BIII).***
- ***Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

HLA-B*5701 SCREENING (Updated December 1, 2007)

Panel's Recommendations:

- ***The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) (AI).***
- ***HLA-B*5701-positive patients should not be prescribed ABC (AI).***
- ***The positive status should be recorded as an ABC allergy in the patient's medical record (AII).***
- ***When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of HSR (CIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

CORECEPTOR TROPISM ASSAYS (Updated January 10, 2011)

Panel's Recommendations:

- ***Coreceptor tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered (AI).***
- ***Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on a CCR5 inhibitor (CIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Initiating Antiretroviral Therapy in Treatment-Naïve Patients (Updated January 10, 2011)

Panel's Recommendations:

- ***Antiretroviral therapy (ART) should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm^3 (AI).***
- ***ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm^3 (A/B*-II).***
- ***ART should be initiated, regardless of CD4 count, in patients with the following conditions: HIV-associated nephropathy (HIVAN) (AII) and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).***
- ***A combination antiretroviral (ARV) drug regimen is also recommended for pregnant women who do not meet criteria for treatment with the goal to prevent perinatal transmission (AI).***
- ***For patients with CD4 counts >500 cells/mm^3, Panel members are evenly divided: 50% favor starting ART at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III).***
- ***Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

* ***Panel members are divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B).***

What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient (Updated January 10, 2011)

Panel's Recommendations:

- ***The Panel recommends the following as preferred regimens for antiretroviral (ARV)-naïve patients:***
  - ***efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) (AI)***
  - ***ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC) (AI)***
  - ***ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC) (AI)***
  - ***raltegravir + tenofovir/emtricitabine (RAL + TDF/FTC) (AI)***
- ***A list of Panel-recommended alternative and acceptable regimens can be found in Table 5a and Table 5b.***
- ***Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance-testing results, and comorbid conditions.***
- ***Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Management of the Treatment-Experienced Patient

VIROLOGIC AND IMMUNOLOGIC FAILURE (Updated January 10, 2011)

Panel's Recommendations:

- ***Assessing and managing an antiretroviral (ARV)-experienced patient experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.***
- ***Evaluation of virologic failure should include an assessment of the severity of the patient's HIV disease, ART history, use of concomitant medications with consideration of adverse drug interactions with ARV agents, HIV RNA and CD4 T-cell count trends over time, and prior drug-resistance testing results.***
- ***Drug-resistance testing should be obtained while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation (AII).***
- ***The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to re-establish virologic suppression (e.g., HIV RNA <48 copies/mL) (AI).***
- ***To design a new regimen, the patient's treatment history and past and current resistance test results should be used to identify at least two (preferably three) fully active agents to combine with an optimized background ARV regimen (AI). A fully active agent is one that is likely to have ARV activity on the basis of the patient's treatment history, drug-resistance testing, and/or a novel mechanism of action.***
- ***In general, adding a single, fully active ARV in a new regimen is not recommended because of the risk of rapid development of resistance (BII).***
- ***In patients with a high likelihood of clinical progression (e.g., CD4 count <100 cells/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits (CI).***
- ***For some highly ART-experienced patients, maximal virologic suppression is not possible. In this case, ART should be continued (AI) with regimens designed to minimize toxicity, preserve CD4 cell counts, and avoid clinical progression.***
- ***Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is not recommended (AI).***
- ***In the setting of virologic suppression, there is no consensus on how to define or treat immunologic failure.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

EXPOSURE-RESPONSE RELATIONSHIP AND THERAPEUTIC DRUG MONITORING (TDM) FOR ANTIRETROVIRAL AGENTS (Updated January 10, 2011)

Panel's Recommendations:

- ***Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult (CIII).***
- ***TDM may be considered in selected clinical scenarios, as discussed in the text below.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Considerations for Antiretroviral Use in Special Patient Populations

ACUTE HIV INFECTION (Updated January 10, 2011)

Panel's Recommendations:

- ***It is unknown if treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit; treatment should be considered optional at this time (CIII).***
- ***Therapy should also be considered optional for patients with HIV seroconversion in the previous 6 months (CIII).***
- ***All pregnant women with acute or recent HIV infection should start a combination antiretroviral (ARV) regimen as soon as possible to prevent mother-to-child transmission (MTCT) of HIV (AI).***
- ***If the clinician and patient elect to treat acute HIV infection, treatment should be implemented with the goal of suppressing plasma HIV RNA to below detectable levels (AIII).***
- ***For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection (AII).***
- ***If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will be helpful in guiding the selection of an ARV regimen that can provide the optimal virologic response; this strategy is therefore recommended (AIII). If therapy is deferred, genotypic resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated (AIII).***
- ***Because clinically significant resistance to protease inhibitors (PIs) is less common than resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in antiretroviral therapy (ART)-naïve persons who harbor drug-resistant virus, a ritonavir (RTV)-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

HIV-INFECTED WOMEN (Updated January 10, 2011)

Panel's Recommendations:

- ***The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents (AI).***
- ***Women taking antiretroviral (ARV) drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method for prevention of unintended pregnancy (AIII).***
- ***In pregnant women, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn (AI).***
- ***Genotypic resistance testing is recommended for all HIV-infected persons, including pregnant women, prior to initiation of ART (AIII) and for women entering pregnancy with detectable HIV RNA levels while on therapy (AI).***
- ***When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).***
- ***Efavirenz (EFV) should be avoided in a pregnant woman during the first trimester or in a woman who desires to become pregnant or who does not or cannot use effective and consistent contraception (AIII).***
- ***Clinicians should consult the most current Health and Human Services (HHS) Perinatal Guidelines when designing a regimen for a pregnant woman (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Considerations for Antiretroviral Use in Patients with Coinfections

HEPATITIS B (HBV)/HIV COINFECTION (January 10, 2011)

Panel's Recommendations:

- ***Prior to intiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication (AIII).***
- ***Because emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV, if HBV or HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen (AI).***
- ***If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (BI). Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen (BII).***
- ***Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients (AII).***
- ***Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against self-discontinuation and carefully monitored during interruptions in HBV treatment (AII).***
- ***If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression (AIII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

MYCOBACTERIUM TUBERCULOSIS DISEASE WITH HIV COINFECTION

(Updated January 10, 2011)

Panel's Recommendations:

- ***The treatment of active tuberculosis (TB) disease in patients with HIV infection should follow the same principles for persons without HIV infection (AI).***
- ***All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately (AI).***
- ***All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART) (AI).***
- ***For patients with CD4 count <200 cells/mm^3, ART should be initiated within 2–4 weeks of starting TB treatment (AI).***
- ***For patients with CD4 count 200–500 cells/mm^3, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).***
- ***For patients with CD4 count >500 cells/mm^3, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).***
- ***Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving ART, with dosage adjustment if necessary (AII).***
- ***If a protease inhibitor (PI)-based regimen is used, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with PIs (AII). Coadministration of rifampin and PIs (with or without ritonavir [RTV] boosting) is <u>not</u> recommended (AII).***
- ***Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS (AIII).***
- ***Treatment support, including directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected patients with active TB disease (AII).***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion